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Which patients with giant cell arteritis will develop cardiovascular or cerebrovascular disease? A Clinical Practice Research Datalink study

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Competing Interest

List of competing interests: 1) Joanna Robson (JR), Joe Maskell (JM), Andrew Hutchings (AH), Nigel Arden (NA), Bhaskar Dasgupta (BD), Willie Hamilton (WH), David Culliford (DC), Akan Emin (AE) and Raashid Luqmani (RL) received a grant from the NIHR Research for Patient Benefit (RfPB) Programme to fund this study. JR, AK, JM, AH, NA, BD, WH, DC, AE and RL had no support from any commercial companies for the submitted work; 2) AK, JM, AH, WH, DC, AE have no relationships with companies which might have an interest in the submitted work in the previous 3 years. NA has the following relationships; consultancies for Flexion (PharmaNet), Lily, Merck, Q-Med, Roche and Smith & Nephew; grants/ grants pending with Novartis, Pfizer, Schering-Plough and Servier and received payment for lectures from Amgen, GSK, NiCox and Smith & Nephew. BD has the following relationships; board membership Roche, Servier, GSK-advisor in GCA; consultancy for Mundi Pharma,GSK,Novartis on PMR. RL has the following relationships; consultancies for Nordic Pharma, Chemocentryx, Human Genome Science, GSK; grants/grants pending with Roche and GSK. 3) JR, AK, JM, AH, NA, BD, WH, DC, AE, RL their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and 4) JR, AK, JM, NA, WH, DC, AE, RL have no non-financial

interests that may be relevant to the submitted work. AH and BD are members of the group that produced the British Society of Rheumatology/ British Health Professionals in Rheumatology 2010 guidelines for the management of giant cell arteritis. BD, AH, RL are members of the group updating these guidelines.

Contributors

All authors contributed to the study proposal, design of the analysis and interpretation of the findings. JR and AK produced the analysis plan. JM was responsible for data extraction. AK and AH undertook the analysis with input from JR and RL. All authors, internal and external, had full access to the data (including statistical reports and tables) in the paper and can take responsibility for the integrity of the data and the accuracy of the data analysis. JR wrote the first draft of the paper which was revised by all authors. JR and AK will act as guarantors.

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ABSTRACT

Objectives: To evaluate the risk of cerebrovascular and cardiovascular disease in patients with giant cell arteritis (GCA), and identify predictors.

Methods: UK Clinical Practice Research Datalink 1991-2010, was used for a parallel cohort study of 5,827 patients with GCA and 37,090 age, gender and location matched controls. A multivariable competing risk model (non-cerebrovascular/cardiovascular related death as the competing risk) determined the relative risk (subhazard ratio, SHR) between patients with GCA compared to background controls for cerebrovascular disease, cardiovascular disease or either. Each cohort (GCA and controls) was then analysed individually using the same multivariable model, with age and gender now present, to identify predictors of cardiovascular or cerebrovascular disease.

Results: Patient with GCA, compared with controls, had an increased risk SHR (95% CI) of cerebrovascular disease (1.45 [1.31-1.60]), cardiovascular disease (1.49 [1.37-1.62]) or either (1.47 [1.37-1.57]). In the GCA cohort, predictors of “cerebrovascular or cardiovascular disease” included increasing age, >80 versus <65 years (1.98 [1.62-2.42]); male gender (1.20 [1.05-1.38]); and socioeconomic status, most deprived quintile versus least deprived (1.34 [1.01-1.78]). These predictors were also present within the non-GCA cohort.

Conclusions: Patients with GCA are more likely to develop cerebrovascular disease or cardiovascular disease than age, gender and location matched controls. In common with the non-GCA cohort, patients who are older, male and from the most deprived, compared with least deprived areas, have a higher risk of cerebrovascular or cardiovascular disease. Further work is needed to understand how this risk may be mediated by specific behavourial, social and economic factors.

INTRODUCTION

Giant cell arteritis (GCA) is the most common form of vasculitis, with the highest incidence of 7.4 per 10,000 person-years in women aged 70–79(1). Cardiovascular and cerebrovascular disease are both increased in patients with GCA(2-4), with a hazard ratio (HR) of 2.06 (95% CI, 1.72 to 2.46) for myocardial infarction and 1.28 (95% CI 1.06 to 1.54) for cerebrovascular accidents in patients versus controls(2). The risk of events is highest in the first year(2, 4), potentially implicating high-dose glucocorticoid use(5, 6), or increased levels of inflammation, as seen in the general population(7) and other rheumatic diseases(8, 9).

Conventional cardiovascular risk factors such as hypertension, hyperlipidaemia and smoking(10) may be implicated in subsequent cardiovascular and cerebrovascular disease in GCA, but this is yet to be proven(2). Smoking is known to increase the likelihood of developing GCA(11). An association between baseline cardiovascular risk factors and severe ischaemic events at the time of diagnosis could provide clues as to the development of later cardiovascular or cerebrovascular disease, but this link is debated(12). A study of 210 Spanish patients with GCA found an increased risk of a severe ischaemic event (defined as a composite endpoint including visual manifestations, claudication of the tongue and jaw, and cerebrovascular accidents) with every conventional cardiovascular risk factor (one of either hypertension, hyperlipidemia, smoking or diabetes), with an odds ratio (OR) of 1.79 (95%CI 1.03 to 3.11)(13). These results were supported by an Italian study of 180 patients which found that a previous history of hypertension and ischaemic heart disease was associated with severe ischaemic events at diagnosis (14). In contrast, a study of 245 GCA and non-GCA subjects from Minnesota, United States, reported no increase in acute coronary syndrome and a lower frequency of cardiovascular risk factors at

diagnosis in GCA patients(15). In addition, a study of 271 patients from the UK demonstrated no associations with pre-existing hypertension or atherosclerosis, but did find an association with social deprivation, with an OR of 4.2 (95% CI 1.3 to 13.6) for a severe ischaemic manifestation, between the most and least deprived quintiles(12). Social deprivation is an emerging risk factor for cardiovascular and cerebrovascular disease in the general population(16), probably mediated by neighborhood deprivation, smoking, physical inactivity and obesity(17, 18) or inequalities in pharmacotherapy(19). There appears to be a geographical variation in the incidence of GCA(20) with higher rates in more affluent areas; whether this effects the development of cardiovascular and cerebrovascular disease in these patients is not known.

The Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database (GPRD), covers a population of 14 million patients from 500 general practices in the UK(21). The available anonymised data(21) includes consultation records, including information on diagnoses and clinical outcomes, and prescription records, stored as computerised Read codes (standardised clinical codes used in General Practice in the UK). The aim of this study is to evaluate the risk and identify predictors of cerebrovascular and cardiovascular disease in patients with GCA.

MATERIALS AND METHODS

Study design using the CPRD

A 20-year parallel cohort (patients with GCA and matched controls) was observed from 01/01/1991 to 31/12/2010 for the outcomes of cerebrovascular and cardiovascular disease. Non-GCA controls were matched to patients with GCA (6:1) on year of birth,

gender and general practice. Ethical approval was given by the CPRD Independent Scientific Advisory Committee.

Outcome measures

We defined three binary outcomes using CPRD Read codes. The first was “cerebrovascular disease” which was compiled using Read codes for stroke or transient ischaemic attack (TIA) or cerebrovascular disease. The second was “cardiovascular disease” and was compiled using Read codes for ischaemic heart disease (IHD) or myocardial infarction (MI) or cardiovascular disease. The third, “cerebrovascular disease or cardiovascular disease” (CDCD) identified patients with either the first outcome or second outcome.

Definition of GCA and controls

Patients with GCA had an incident GCA Read code between 01/01/1991 and 31/12/2010, and ≥2 prescriptions for oral glucocorticoids, as per previous validated methods of confirming the diagnosis of GCA within the CPRD (20). Patients were aged ≥40(20) with at least 12 months of CPRD defined up-to standard (UTS) data prior to their index diagnosis; patients were excluded if they had a previous diagnosis of cerebrovascular or cardiovascular disease. Controls did not have a diagnosis of GCA or polymyalgia ever recorded in the CPRD, and they had at least 12 months UTS follow-up recorded prior to the date of diagnosis of the matched GCA patient; controls were excluded if they had a previous diagnosis of cerebrovascular or cardiovascular disease.

Cardiovascular risk factors

Read codes were used to identify a history of hyperlipidaemia and hypertension. Prescriptions for at least 75% of the year, in any year out of the previous five prior to diagnosis of GCA or the matched time point in controls, were needed to confirm previous lipid-lowering, antihypertensive or diabetic treatment. Previous diabetes was flagged by medical Read codes; a prescription of oral diabetic medications for at least 75% of the year or two or more prescriptions of injectable insulin or insulin needles, in any year out of the previous five. All patients diagnosed with GCA are routinely treated with glucocorticoids, therefore their use was not included as a covariate. Smoking and alcohol variables were categorised as ‘current’, ‘ex’ and ‘never’. The body mass index (BMI) variable was the closest recorded before the start of the exposed to risk period. The Index of Multiple Deprivation (IMD) combines information from seven domains of deprivation: income; employment; education, skills and training; health deprivation and disability; crime; barriers to housing and services and living environment, to provide a set of relative measures of deprivation for small areas, or neighbourhoods (known as Lower-layer Super Output Areas) across England(22). IMD data was provided in quintiles, from quintile 1 (least deprived) to quintile 5 (most deprived).

Analysis

Descriptive statistics were used to compare patient characteristics of the GCA and control cohorts. The t-test was used for normal continuous data, the rank sum test for non-normal data and the chi square test for categorical data.

The (crude) risk of incident cardiovascular or cerebrovascular disease with GCA compared with non-GCA cohorts was then calculated. Patients with GCA were ‘exposed to risk’ of cerebrovascular disease or cardiovascular disease from the date

of diagnosis to the earliest of the endpoints: date of death, transfer out (left the study), end of study date or date of cerebrovascular disease or cardiovascular disease diagnosis (the earlier date was used for the combined outcome CVD). Non-GCA controls were exposed to risk from the same date as their corresponding matched patient with GCA, with the same endpoints.

Cumulative incidence function plots stratified by GCA status, gender, smoking status and socioeconomic status were used to describe the probability of combined CVD events over time and were tested using the log rank test.

For each outcome, the relative risk (subhazard ratio, SHR) between GCA and non-GCA controls was determined using a competing risk model using non-cerebrovascular/cardiovascular death as the competing risk. Univariable models were described, then a full multivariable model adjusting for risk factors (BMI, smoking, alcohol, deprivation, hyperlipidaemia, hypertension, anti-hypertensives, diabetes and lipid-lowering medications); age and gender were excluded as the cohorts were matched. Two way interaction effects between GCA status and the vascular risk factors (and each other) were also investigated. Each interaction term was individually tested in the initial multivariable model; significant terms ($p<0.1$) were then used to build the final multivariable model. A sub-group analysis for each of the thirteen geographical regions was also performed to investigate variations in the relative risk of cardiovascular or cerebrovascular disease.

Competing risk of variables in GCA and non-GCA cohorts

Each cohort was then analysed individually using the same multivariable model, with age and gender now present in the model to identify predictors. All multivariable survival models were tested for the proportional hazards assumption using Schoenfeld

residuals. All statistical analyses were performed using Stata SE v12.0 (StatCorp, College Station, TX, USA).

Missing data

Multiple imputation was used to account for the missing values for BMI (29.5%), smoking (14.3%), alcohol (23.2%) and IMD (45.2%) using imputation by chained equations(23). The algorithm generated 10 imputed data sets; estimates were pooled using Rubin's combination rules for analysis(24).

RESULTS

Participants

5,827 patients with GCA and 37,090 matched non-GCA controls met our inclusion/exclusion criteria and were used in the analysis (Figure 1).

Descriptive statistics

In both cohorts the mean (standard deviation (SD)) age was 71 years (10.7), around 73% were female and one in nine women were from the most deprived areas (11% IMD quintile 5) (Table 1). Patients from the GCA cohort, compared with those from the non-GCA cohort, were more likely to have a previous history of hyperlipidaemia (4.8% versus 3.8%), hypertension (27.0% versus 25.2%), use of anti-hypertensive agents (36.7% versus 33.2%), diabetes (8.8% versus 7.9%) and lipid-lowering medication use (12.1% versus 11.5%). They were more likely to be current smokers (18.4% versus 15.9%) and less likely to consume alcohol (72.8% versus 75.0%) (Table 1).

The relative risk of cerebrovascular or cardiovascular disease

The risk of cerebrovascular disease, cardiovascular disease or “cerebrovascular or cardiovascular disease” was higher in patients with GCA than non-GCA (Table 2). The largest difference in risk was observed in the “cerebrovascular or cardiovascular disease” analysis where the risk in the GCA and non-GCA cohort was 18.3% and 12.6% respectively, giving a crude risk ratio of 1.45.

In the multivariable competing risk model, the subhazard ratio for “cerebrovascular or cardiovascular disease” was 1.47 (95%CI 1.37 to 1.57); cerebrovascular disease was 1.45 (95%CI 1.31 to 1.60) and cardiovascular disease was 1.49 (1.37 to 1.62).

The models were adjusted for risk factors (as described earlier). No two way interaction effects were observed between GCA status and the covariates ($p>0.1$ for all interactions). However, we included significant two way interaction terms between the covariates themselves; hypertension and anti-hypertensives, hypertension and lipid-lowering medications, hypertension and hyperlipidaemia. Schoenfeld residuals showed the proportionality assumption was not violated.

No regional variations were seen on subgroup analysis when the multivariable competing risk model for “cerebrovascular disease or cardiovascular disease” was run for each region in the UK (Figure 3).

Predictors of cerebrovascular disease and cardiovascular disease

Combined outcome of cerebrovascular and cardiovascular disease

In the GCA cohort, increasing age, [SHR 1.61 for patients aged 65-70 versus ≤65 (95%CI 1.31 to 1.99), being male [SHR 1.20 (95%CI 1.05 to 1.38)], and being in the most versus the least deprived quintile [SHR 1.34 (95% CI 1.10 to 1.78)] were risk

factors for the combined outcome of “cerebrovascular and cardiovascular disease”. In the non-GCA cohort, increasing age [SHR 1.76 for patients aged 65-70 versus ≤65 (95%CI 1.58 to 1.98), being male [SHR 1.34 (95%CI 1.25 to 1.43)] and in the most versus the least deprived quintile [SHR 1.21 (95%CI 1.08 to 1.37)], current smoking [SHR 1.18 (95%CI 1.08 to 1.29), previous history of hypertension [SHR 1.78 (95%CI 1.59 to 1.99)] and diabetes [SHR 1.22 (95%CI 1.10 to 1.36), were risk factors for the combined outcome of “cerebrovascular and cardiovascular disease”, whilst previous prescription of anti-hypertensives were protective [SHR 0.68 (95%CI 0.61 to 0.79) (Table 3).

Predictors of the individual outcomes of cardiovascular disease or cerebrovascular disease in the GCA and non-GCA cohorts are detailed in Table 3.

Cumulative incidence plots also demonstrated differences in the risk of “cardiovascular or cerebrovascular disease” when stratified by GCA versus non-GCA diagnosis (increased risk with GCA), gender (increased risk amongst males with GCA), smoking (increased risk amongst current smokers with GCA) and socioeconomic status (increased risk amongst patients from most deprived areas and GCA) (Figure 2).

DISCUSSION

Patients with GCA are fifty percent more likely to develop incident cerebrovascular or cardiovascular disease than age, gender and practice matched controls, in line with previous studies (2, 4). This effect is independent of conventional cardiovascular risk factors and social deprivation. This study provides new information about the importance of cardiovascular risk factors within this population. Lower socioeconomic status, older age (≥65), and being male are all independent predictors of “cerebrovascular or cardiovascular disease” within the GCA cohort. A history of

hypertension is also an independent risk factor for developing cardiovascular disease in GCA patients. A wider number of predictors of cardiovascular and cerebrovascular disease was noted in the non-GCA cohort (as per the GCA cohort but with the addition of previous diabetes as predictive, and lipid lowering medications and anti-hypertensives as protective). This may be purely due to greater statistical power in the non-GCA cohort, as suggested by the lack of any interactions between the main exposure (GCA or non-GCA) and any of the conventional cardiovascular risk factors within the overall competing risk analysis. Previous studies in GCA have not found an association between conventional cardiovascular risk factors and cardiovascular outcomes (15), or other ischaemic disease(12), but sample sizes were relatively small at 245 and 271 patients respectively in these studies so may have been similarly underpowered. In relation to socioeconomic status, this is the first study to show an association between higher levels of deprivation and the development of cardiovascular or cerebrovascular disease in GCA. Social deprivation is known to be associated with cardiovascular disease within the general population(17); this study demonstrates that this is also true of patients with GCA. Further work is needed to understand how this risk may be mediated by specific behavourial, social and economic factors. For example, there can be significant delays in the initial diagnosis and management of GCA, and this may be associated with an increased incidence of irreversible ischaemic complications at diagnosis(25). This study did not identify any regional variations in terms of the risk of developing cerebrovascular or cardiovascular disease, this may be interpreted as being reassuring but more work is needed to exclude an effect of differing local referral and management protocols.

This is a large cohort study of patients with incident GCA (n=5827) with prospectively recorded data including baseline risk factors and cerebrovascular and cardiovascular

disease outcomes, enabling the identification of risk factors within this population. However, there are limitations. Despite the size of this cohort, greater numbers still may be needed to demonstrate the full range of cardiovascular risk factors(2) in GCA patients. It is also not possible to identify biopsy-positive patients or classify them according to the 1990 American College of Rheumatology (ACR) criteria(26) within the CPRD; instead, a combination of diagnostic code and glucocorticoid prescriptions were used to identify GCA patients (20). This may have resulted in patients being misclassified as having GCA; although inclusion of biopsy negative patients may underestimate rather than overestimate any potential association between GCA and cerebrovascular or cardiovascular disease. There is also the potential for vascular disease to be more commonly suspected and diagnosed in patients with GCA, because they are under closer medical follow up post-diagnosis. Read codes were used to define hypertension and hyperlipidaemia, but not whether patients had an elevated systolic or diastolic blood pressure or the category of hyperlipidamia, which may be important for differing cardiovascular and cerebrovascular outcomes(27, 28). The proportion of missing data that was imputed, particularly for IMD (45%), was large. We maintained efficiency by increasing the number of imputed sets from 5 (most commonly used) to 10. However, this process was based on the assumption that values were missing at random. If the values were missing not at random (untestable in the CPRD), our estimates of direct and indirect effects of IMD on CVD would be affected and this is a limitation of the analysis. Treatment with glucocorticoids was considered as being part of the diagnosis of GCA in this analysis; their use has however been implicated in cardiovascular and cerebrovascular disease and therefore needs future investigation (29, 30). In the general population, there is an inverse relationship between physical activity and cardiovascular disease, with a median risk

reduction of 30-35% in the most versus the least active groups(31) . Information on the amount and intensity of physical activity is not collected through the CPRD which is another limitation of this study.

In practice, this study suggests that clinicians should be alerted to the fact that patients with GCA are at increased risk of cardiovascular and cerebrovascular disease, particularly if they have pre-existing hypertension, are older, male or live in an area of higher social deprivation. It seems reasonable for patients with other cardiovascular risk factors to also be considered as higher risk, but this cannot be categorically stated from this study, possibly due to lack of power, despite the large sample size. Further work is needed to identify the causal pathways involved in the association between social deprivation and increased cardiovascular and cerebrovascular disease in patients with GCA, so that targeted interventions to address this disparity can be developed.

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